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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 08/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,154	COX ET AL.	
	Examiner	Art Unit	
	Betty Lee, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/08/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,15,16,19,20,22-26,28-33,37,38,40-46,52,53 and 57-66* is/are pending in the application.

4a) Of the above claim(s) *8-10,12,14,17,18,21,34-36,39,47-51 and 54-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,15,16,19,20,22-26,28-33,37,38,40-46,52,53,57-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-10,12,14-26,28-33 and 37-66* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I in the reply filed on 4/08/05 is acknowledged. Applicant elected with traverse, the species (32), directed to EPO is also noted. Applicants traverse on the grounds that the fusion proteins of the present invention are linked by the common special technical feature of being Ig fusion proteins in which a soluble protein (a growth factor or cytokine and specifically, members of the growth hormone supergene family) is joined to an Ig domain in a specific manner that results in a fusion protein that effectively preserves the biological activity of the natural soluble protein as compared to any previously described fusion protein using these types of soluble proteins. The species which include growth hormone, prolactin, placental lactogen, cytokines, oncostatin M, ciliary neurotrophic factor, leukemia inhibitory factor, alpha interferon, beta interpheron, gamma interferon, omega interferon, tau interferon, G-CSF, cardiotrophin-I, macrophage colony stimulating factor, EPO, etc have varied physiological functions, properties and structures. The species lack unity of invention because the soluble proteins cited in the claims can be joined with or without a linker to an Ig domain. In addition, the soluble proteins encompassed in some of the claims can be joined without an Ig domain. Any conditions not required by all claims cannot form a basis of unity. Furthermore, any aspects of the invention e.g. peptide linkers or immunoglobulin fusion proteins that are taught by prior art cannot form the basis of unity. Applicants' arguments have been considered and are not found persuasive because of the above stated reasons. Therefore, the requirement for species election is maintained.

Claims 1-7, 15, 42, 43, 52, 62-65 are generic. Claims 1-7, 15,16, 19, 20, 22-26, 28-33, 37, 38, 40-45, 52, 53, 57-66 are under consideration. Claims 8-10, 12,14, 17, 18,21, 34-36, 39, 47-51 and 54-56 are withdrawn from consideration as being drawn to a non-elected invention or species.

Claim Objections

2. Claims 16, 25, 41 and 53 are objected to for reading on non-elected species, as generic claim is not allowable.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 24, 26, 38, 43, 44 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1 and 2 cite that the 'Ig domain' does not contain a variable region. It is unclear if the fusion protein may contain a variable region or whether this applies only to the 'Ig domain'.

The phrase in claim 2 cites 'the cytokine is not IL-10 or an interferon'. It could mean that 'the cytokine is not IL-10, and the interferon is part of the group'. It could also mean a cytokine that is not interferon. As the meaning is unclear, the claim is indefinite. The phrase 'active variant of' is unclear because the phrase could mean an'active variant of interferon or everything in the group'. Therefore the claim is indefinite.

Claims 38 and 44 cite the phrase 'EPO-dependent *in vitro* bioassay'. The phrase is indefinite because depending on what assay is used, the EC_{50} will vary.

Claims 24 and 52 are not further limiting as the claims are to a protein and not to a composition. Therefore, the claims are indefinite because a multimer must, by definition, comprise a monomer; it is not clear how applicants intend otherwise. Claims 26 and 43 are rejected as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the expression vector is missing and the method of protein expression in the cells is not mentioned.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6, 7,24, 25, 28-31, 37 and 43 are rejected under 35 U.S.C. 102(b) as being unpatentable over Sytkowski, *et al* WO 9902709. Sytkowski, *et al* teaches the construction and expression of Epo-Ig fusion proteins. They described on pg 3, lines 24-31, pg 4, lines 1-2 "in one embodiment of the present invention, DNA encoding erythropoietin, or an erythropoietin-like molecule, is fused at its N-terminus to DNA encoding an immunoglobulin constant region. In another embodiment of the present invention, DNA encoding erythropoietin, or an erythropoietin-like molecule, is fused at its C-terminus to the DNA encoding an immunoglobulin constant region. The fused sequence is expressed in competent cells, resulting in production of an erythropoietin/immunoglobulin fusion protein that has biological activity."

Sytkowski, *et al* further teaches on pg 15, lines 14-19, " that the entire immunoglobulin heavy chain constant region (CH1-hinge-CH2-CH3) can be fused to the erythropoietin molecule. Alternatively, the immunoglobulin constant region can comprise all, or a portion of the hinge region, the CH2 domain and the CH3 domain. The immunoglobulin constant region can also comprise the CL1 domain of an immunoglobulin light chain". The reference teaches on pg 16, lines 30-32, that the protein, e.g., erythropoietin, can be attached (e.g., joined or linked) to the hinge via either its amino-or carboxyl-terminus. Claims 1 and 6 are anticipated by the reference because the fusion protein contains an Ig domain and a growth factor and the Ig domain is selected from the group consisting of IgG-Fc, IgG-C_H and IgG-C_L. Claim 7 cites 'the soluble protein is a member of the growth hormone (GH) supergene family' and this limitation is met by the reference.

They teach on pg 17, lines 5-16 that the "nucleic acid sequence encoding erythropoietin and the nucleic acid sequence encoding the immunoglobulin constant region must be in the correct translational reading frame. The erythropoietin nucleic acid sequence can be joined directly to, e.g., the hinge region nucleic acid sequence, or, alternatively, additional nucleotides encoding a flexible protein sequence, (e.g., about 1

to about 20 amino acids) can be inserted prior to the hinge region nucleic acid sequence, as long as the inserted nucleotides do not interfere with the biological activity of the expressed fusion protein or do not confer any undesired activities, e.g., such as antigenity." Although, Sytkowski, *et al* describes in detail the construction and expression of a mouse EPO-Ig fusion protein, their specification does not limit the EPO-Ig fusion protein to one species.

Claim 24 refers to the composition of 'the fusion protein as dimeric' which is anticipated by Sytkowski, *et al* on pg 3, lines 17-20 which teaches that these erythropoietin/Ig fusion proteins are dimers (if two monomers are joined). The limitations of claim 25 cite the 'soluble protein is selected from the group consisting of G-CSF, EPO and interleukin-11', which is met by the reference. Claim 28 cites the nucleic acid encoding the fusion protein and claim 43 cites the method of producing a fusion protein, which are anticipated by the above reference. In addition, claims 29 refers to the transformed host cell, while claim 30 defines the host cell as 'eukaryotic' and claim 31 cites a 'mammalian' cell. The above limitations are met by the reference on pg 18, lines 27-30. The reference further teaches on pg 21, lines 14-31, the pharmaceutical composition comprising the fusion protein and a pharmaceutically acceptable carrier and anticipates claim 37.

Claims 15, 16, 19, 20, 40 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Sytkowski, US Patent 6242570. Sytkowski teaches a multimeric fusion protein comprising two or more members of erythropoietin joined with or without a peptide linker, column 2, lines 1-11. The reference teaches 'the proteins of the present invention can be fused directly to another protein, or can be fused via a linker, e.g., a peptide linker.' Claim 15 cites a 'homomultimeric fusion protein comprising two or more copies of the Growth Hormone (GH) supergene family joined without an intervening linker' while claim 40 cites a 'homomultimeric fusion protein, comprising two or more copies of erythropoietin joined by at least one peptide linker'. Sykowski in column 2, lines 32-49 gives a list of GH supergene family and further teaches that the fusion

proteins can be joined with or without a linker in column 3, lines 28-33. Therefore, the reference meets the limitations of the claims.

Claims 19, 20 and 57 which further limits GH family member to 'EPO' and a 'dimeric EPO fusion protein'. The limitations of the claims are met by the above reference in column 3, lines 41-44.

Sytkowski teaches in column 4, lines 52-67, that the linker amino acids may include serine, glycine and asparagine and 'the length may vary without significantly affecting the biological activity of the fusion protein'. Column 4, lines 57-58, teaches that 'threonine and alanine may also be used in the linker sequence'. Therefore, this reference anticipates claims16 and 40.

Claim 41 is rejected under 35 U.S.C. 102(b) as being anticipated by Amoresano, *et al* Glycobiology 8:779-790, 1998. Amoresano, *et al* teaches the human GM-CSF/EPO fusion protein and the peptide linker comprising of glycine, serine and alanine residues. Claim 41 cites a 'multimeric fusion protein comprising two or more different members of GH supergene family joined by at least one peptide linker that consists of a mixture of two or more amino acid residues selected from the group consisting of: glycine, serine, alanine and threonine residues'. GM-CSF and EPO are both members of GH supergene family. The reference also discloses an eight amino acid peptide sequence comprising of glycine, serine and alanine on pg 788, column 2, lines 12-15 and in Fig 1. Therefore, the limitations of claim 41 are anticipated by Amoresano, *et al.*

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 2, 26, 42, 45, 46, 52, 53, 62-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sytkowski, *et al* WO 9902709 in view of Curtis, *et al* US Patent 5073627.

Sytkowski, *et al* (WO 9902709) teaches the construction and expression of the Epo-Ig fusion protein including the use of linkers to join the two proteins. It does not explicitly discuss the peptide linkers that can be used to join a fusion protein.

Curtis, *et al* teaches a multimeric fusion protein comprising two or more members of the Growth Hormone (GH) supergene family (GM-CSF and IL-3) joined with or without a peptide linker, column 6, lines 50-60. Column 7, lines 7-12 teaches that the length of linker sequence may vary from 1-500 amino acids in length and in the 'most preferred aspects the linker sequence is from 1-20 amino acids in length'. Curtis, *et al* teaches that amino acids useful for linkers include serine and glycine in column 7, lines 15-20.

Claim 2 cites the fusion protein is 'joined at its carboxy-terminus by a peptide linker'. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of Sytkowski, *et al* (WO 9902709) and Curtis, *et al* and using a human cDNA to construct the Epo-Ig fusion protein and adding a peptide linker as disclosed by Curtis, *et al*. It would have been obvious to use these different forms of peptide linkers to join the fusion protein because linkers add flexibility. A person of ordinary skill in the art would have been motivated to make a human EPO-

Ig fusion protein with peptide linkers because Sytkowski, *et al* teaches the use of linkers and Curtis, *et al* teaches that glycine serine makes a good flexible linker and reasonably would have expected success because the teachings are well known in the art.

Claim 26 cites a method of purifying the fusion protein while claim 42 limits the composition of the fusion protein as 'dimeric'. Claim 45 refers to 'the Ig domain' and claim 46 refers to the 'protein as a member of the GH supergene family'. Claim 52 cites 'the protein is essentially free of monomeric fusion protein' and claim 53 cites the protein is selected from the group consisting of G-CSF, EPO and interleukin-11'. Both these references teach the purification of fusion proteins. Claims 62 cites 'the peptide linker consists of a mixture of glycine and serine residues' Claim 63 limits the peptide linker to 'no more than 50 amino acids' while claim 64 limits it to 'no more than 22 amino acids. Furthermore, claim 65 limits the peptide linker to 'between 2 and 7 amino acids in length'. Since Curtis teaches 1-500 and 1-20 amino acids are suitable for linkers, any of the recited lengths are obvious in view of Curtis who teaches lengths consistent with the claims, and that it is routine to determine acceptable linker lengths. The person of ordinary skill in the art would have been motivated to modify the teachings of Sytkowski, *et al* and add peptide linkers of varying length consisting of serine and glycine residues in different combinations to increase the flexibility of the fusion proteins.

Claims 2, 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sytkowski, *et al* WO 9902709 in view of Mapelli, *et al* US Patent 5519115. Sytkowski, *et al* (WO 9902709) teaches the construction and expression of the Epo-Ig fusion protein including the use of linkers to join the two proteins. It does not teach the use of SerGly linker specifically. Mapelli, *et al* teaches in column 25, lines 1-14 the construction of peptide linkers containing between 1 and 5 amino acids comprising of Ser and Gly residues and gives an example of Ser-Gly-Gly-Ser. Column 27, lines 1-30, describe the different combinations of amino acids that are recommended for peptide bridges. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Sytkowski, *et al* with the use of linkers taught by Mapelli, *et al* because the peptide linkers have been shown to provide

flexibility to fusion proteins. The person of ordinary skill in the art would have been motivated to make those modifications because these types of linkers are known to be adaptable to any type of fusion protein and would have expected success because the techniques involved are standard practice in the art.

Claims 22, 23, 58, 59 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sytkowski, US Patent 6242570 in view of Mapelli, *et al* US Patent 5519115. Sytkowski teaches in column 4, lines 52-67, that the linker amino acids may include serine, glycine and asparagine and 'the length may vary without significantly affecting the biological activity of the fusion protein'. It does not teach the exact sequences as cited in claims 22, 23, 58,59 and 66. Mapelli, *et al* teaches in column 25, lines 1-14 the construction of peptide linkers containing between 1 and 5 amino acids comprising of Ser and Gly residues and gives an example of Ser-Gly-Gly-Ser, which are similar to the claims. Furthermore, Mapelli *et al* gives an example in column 27, lines 20-23 of a dipeptide linker consisting of ser-gly amino acids. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Sytkowski with the use of linkers taught by Mapelli, *et al* for the reasons stated above.

Claims 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amoresano, *et al* Glycobiology 8:779-790, 1998 in view of Mapelli, *et al* US Patent 5519115. Amoresano, *et al* teaches the human GM-CSF/EPO fusion protein and the peptide linker comprising of glycine, serine and alanine residues. It does not teach the exact sequences of claims 60 and 61. Mapelli, *et al* teaches in column 25, lines 1-14 the construction of peptide linkers containing between 1 and 5 amino acids comprising of Ser and Gly residues and gives an example of Ser-Gly-Gly-Ser, which are similar to the claims. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Amoresano, *et al* with the use of linkers taught by Mapelli, *et al* for the reasons stated above.

Claims 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sytkowski, *et al* WO 9902709 in view of Strom, *et al* WO9902711. Sytkowski, *et al* (WO 9902709 A1) teaches the construction and expression of the Epo-Ig fusion protein. The reference teaches on pg 25, line 31 and pg 26, lines 1-3, the use of protein A-sepharose column for purifying the fusion protein. It does not teach the use of size-exclusion chromatography. Strom, *et al* teaches on pg 21, lines 11-17, the cloning, expression and purification of human EPO fusion proteins which includes column chromatography as a step e.g. size-exclusion chromatography. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Sytkowski, *et al* and incorporate size-exclusion chromatography as taught by Strom, *et al*. The person of ordinary skill in the art would have been motivated to make the modification as evidenced by Strom, *et al*.

Claims 38 and 44 are rejected under 35 U.S.C. 102 as anticipated by, or in the alternative, under 35 U.S.C. 103(a) as being unpatentable over Sytkowski, *et al* WO 9902709 A1. Sytkowski, *et al* WO 9902709 A1 teaches the construction and expression of the Epo-Ig fusion protein. Both claims 38 and 44 cite 'the fusion protein has an EC_{50} of less than about 1000ng/ml in an Epo-dependent in vitro bioassay'. Sytkowski is silent with respect to the EC_{50} of the protein. However, as Sytkowski's protein meets all the structural limitations of the claims and there appears to be no critical difference between Sytkowski's protein and that claimed, and as the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Betty Lee, Ph.D. whose telephone number is (571) 272-8152. The examiner can normally be reached on M-F 9 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BLL

LORRAINE SPECTOR
PRIMARY EXAMINER